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Ambient Water Quality Criteria Tetrachloroethylene

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TETRACHLOROETHYLENE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

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CRITERION DOCUMENT

TETRACHLOROETHYLENE

Criteria

Aquatic Life

For tetrachloroethylene, the criterion to protect freshwater aquatic life, as derived using procedures other than the Guidelines, is 310 µg/l as a 24-hour average and the concentration should not exceed 700 µg/l at any time.

For tetrachloroethylene the criterion to protect saltwater aquatic life as derived using the Guidelines is 79 µg/l as a 24-hour average and the concentration should not exceed 180 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to tetrachloroethylene through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of tetrachloroethylene estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 2.0 µg/l, 0.20 µg/l, and 0.020 µg/l, respectively.

BIBLIOGRAPHIC INFORMATION

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Ambient Water Quality Criteria: Tetrachloroethylene.

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for tetrachloroethylene. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or techno , ...

KEYWORDS: *Water quality, *Toxicology, *Tetrachloroethylene, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Ethylene/tetrachloro.

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Introduction

Tetrachloroethylene (1,1,2,2-tetrachloroethylene, perchloroethylene, PCE) is a colorless, nonflammable liquid used primarily as a solvent in the dry cleaning industries. It is used to a lesser extent as a degreasing solvent in metal industries (Windholz, 1976).

PCE has the molecular formula C_2Cl_4 and a molecular weight of 165.85. Other physical properties of PCE include a melting point of -23.25 degrees C, a density of 1.623 g/ml, a vapor pressure of 19 mm Hg, a water solubility of 150 µg/ml and an octanol/water partition coefficient of 339 (log P = 2.53) (Patty, 1963, U.S. EPA, 1978). The log P value indicates that PCE has a high affinity for lipid material and may bioaccumulate in animals.

Perchloroethylene is widespread in the environment, and is found in trace amounts in water, aquatic organisms, air, foodstuffs, and human tissue. (McConnell, et al. 1975).

The highest environmental levels of PCE are found in the commercial dry cleaning and metal degreasing industries (Natl. Inst. Occup. Safety Health (NIOSH), 1976). The current level of PCE permissible in U.S. working environments is 670 mg/m^3 (100 ppm) (NIOSH, 1976).

Although PCE is released into water via aqueous effluents from production plants, consumer industries, and household sewage, its level in ambient water is reported to be minimal due to its high volatility. PCE has been detected at levels below 1 µg/l in waters surrounding chlorinated hydrocarbon production plants in England (Pearson and McConnell, 1975) and in U.S. surface waters (Ewing and Chian, 1977).

In the laboratory, PCE has been demonstrated to be toxic to aquatic organisms (Alexander, et al. 1978; Pearson and McConnell, 1975; U.S. EPA, 1978). The primary toxic effect observed in human and non-human mammals after acute or chronic inhalation of PCE is central nervous system depression (U.S. EPA, 1975; Patty, 1963; NIOSH, 1976). PCE has also been reported to be hepatotoxic to mammals (U.S. EPA, 1975; Kylin, et al. 1965; Rowe, et al. 1952) and carcinogenic in mice (Natl. Cancer Inst., 1976); thus, there is concern about its toxicity to humans.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The data base for tetrachloroethylene and freshwater organisms indicates that the bluegill and fathead minnow are about as sensitive as Daphnia magna. The data on an alga indicate that that species is much more resistant. Compared to the dichloroethylenes and trichloroethylene, tetrachloroethylene is more acutely toxic to fish and invertebrate species.

Acute Toxicity

Alexander, et al. (1978) compared the toxicity of tetrachloroethylene to the fathead minnow using static unmeasured and flow-through measured procedures; the unadjusted 96-hour LC50 values were 21,400 and 18,400 µg/l, respectively (Table 1). The bluegill (U.S. EPA, 1978) is equally sensitive. The LC50 values for the fathead minnow after adjustment (Table 1) are more different than before adjustment, but the two test results are insufficient in number to conclude whether or not the Guideline's adjustment factors for test methods are appropriate in this instance. When the geometric mean of the adjusted values is divided by the Guidelines species sensitivity factor of 3.9 the result, 2,600 µg/l, is the Final Fish Acute Value (Table 1).

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Daphnia magna has been tested with tetrachloroethylene (U.S. EPA, 1978) and the adjusted 48-hour EC50 is 15,000 µg/l. Division by the sensitivity factor of 21 results in the Final Invertebrate Acute Value of 700 µg/l (Table 2), which also becomes the Final Acute Value.

The data on acute static tests with the bluegill under similar conditions (U.S. EPA, 1978) in this and other documents on chloroethylenes show a correlation between increasing chlorination and toxicity. The 96-hour LC50 values for this species are 73,900 and 135,000 µg/l for 1,1- and 1,2-dichloroethylene, respectively, 44,700 µg/l for trichloroethylene and 12,900 µg/l for tetrachloroethylene. These results indicate an increase in the lethal effect on bluegills with an increase in chlorination. The correlation with Daphnia magna toxicity is not as clear. The 48-hour LC50 values are 79,000, 85,200, and 17,700 µg/l for 1,1-dichloroethylene, trichloroethylene, and tetrachloroethylene, respectively.

Chronic Toxicity

Chronic test data are not available for freshwater species.

Plant Effects

No adverse effects on chlorophyll a or cell numbers or the alga, Selenastrum capricornutum, were observed at exposure concentrations as high as 816,000 µg/l (Table 3).

Residues

The bioconcentration factor for bluegill (U.S. EPA, 1978) was determined to be 49 using ^{14}C-tetrachloroethylene with verification by thin-layer chromatography (Table 4.) Equilibrium was reached within 21 days and the depuration rate was rapid with a half-life of less than one day. Using similar methods (U.S. EPA, 1978) the bioconcentration factor for trichloroethylene was 17, not appreciably different than that for tetrachloroethylene. No comparable data are available for any dichloroethylene.

Miscellaneous

Alexander, et al. (1978) also determined a 96-hour EC50 based on loss of equilibrium by the fathead minnow. This occurred at 14,400 µg/l (Table 5), a concentration slightly lower than the 96-hour LC50 values of 18,400 and 21,400 µg/l for the same species.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 2,600 µg/l

Final Invertebrate Acute Value = 700 µg/l

Final Acute Value = 700 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = greater than 820,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 820,000 µg/l

0.44 x Final Acute Value = 310 µg/l

No freshwater criterion can be derived for tetrachloroethylene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

However, results obtained with tetrachloroethylene and trichloroethylene and saltwater and freshwater organisms respectively indicate how a criterion may be estimated.

For tetrachloroethylene and saltwater organisms and for trichloroethylene and freshwater organisms the Final Chronic Value based on data for invertebrate species is greater than 0.44 times the Final Acute Value. Therefore, it seems reasonable to estimate a criterion for tetrachloroethylene and freshwater organisms using 0.44 times the Final Acute Value.

To estimate a criterion for tetrachloroethylene, the maximum concentration is the Final Acute Value of 700 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For tetrachloroethylene the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 310 µg/l as a 24-hour average and the concentration should never exceed 700 µg/l at any time.

Table 1. Freshwater fish acute values for tetrachloroethylene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, Pimephales promelas	FT	M	96	18,400	18,400	Alexander, et al. 1978
Fathead minnow, Pimephales promelas	S	U	96	21,400	11,700	Alexander, et al. 1978
Bluegill, Lepomis macrochirus	S	U	96	12,900	7,000	U.S. EPA, 1978

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 10,134 µg/l $\quad \frac{10,134}{3.9} = 2,600$ µg/l

Lowest value from a flow-through test with measured concentrations = 18,400 µg/l

Table 2. Freshwater invertebrate acute values for tetrachloroethylene (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Cladoceran, Daphnia magna	S	U	48	17,700	15,000

* S = static

** U = unmeasured

Geometric mean of adjusted values = 15,000 ug/l $\frac{15,000}{21}$ = 700 ug/l

Table 3. Freshwater plant effects for tetrachloroethylene (U.S. EPA, 1978)

Organism	Effect	Concentration (ug/l)
Alga, *Selenastrum capricornutum*	Chlorophyll *a* 96-hr EC50	>816,000
Alga, *Selenastrum capricornutum*	Cell number 96-hr EC50	>816,000

Table 4. Freshwater residues for tetrachloroethylene (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
Bluegill, *Lepomis macrochirus*	49	21

Table 5. Other freshwater data for tetrachloroethylene (Alexander, et al. 1978)

Organism	Test Duration	Effect	Result (ug/l)
Fathead minnow, *Pimephales promelas*	96-hr	Loss of equilibrium, EC50	14,400

SALTWATER ORGANISMS

Introduction

Acute and chronic tests have been conducted with the mysid shrimp and the chronic value is 0.044 of the 96-hour LC50; this suggests a very substantial accumulative chronic toxicity. The saltwater alga, Skeletonema costatum, is much more resistant, a pattern consistent with that for freshwater organisms. Compared to 1,1-dichloroethylene, tetrachloroethylene is much more toxic to the mysid shrimp.

Acute Toxicity

The mysid shrimp has been tested (U.S. EPA, 1978) using static, unmeasured procedures and the unadjusted 96-hour LC50 is 10,200 µg/l (Table 6). Since no acute data are available for saltwater fish, the Final Invertebrate Acute Value for the mysid shrimp (180 µg/l) also becomes the Final Acute Value. This conclusion is supported by the fact that the 96-hour LC50 value for sheepshead minnow is between 29,400 and 52,200 µg/l (Table 9).

The 96-hour LC50 for the mysid shrimp and tetrachloroethylene is, as stated above, 10,200 µg/l (U.S. EPA, 1978). The 96-hour LC50 for the same species under similar test conditions (U.S. EPA, 1978) is 224,000 µg/l for 1,1-dichloroethylene. As was suggested in the freshwater part of this document, acute toxicity of these structurally related compounds increases with increases in chlorination although the data for Daphnia magna are less consistent.

Chronic Toxicity

The chronic value for the mysid shrimp is 448 µg/l (Table 7) and 0.044 of the 96-hour LC50 for the same species. When divided by the Guidelines species sensitivity factor of 5.1, this value results in a Final Invertebrate Chronic Value of 88 µg/l. Since no chronic data are available for saltwater fish, 88 µg/l also becomes the Final Chronic Value.

Plant Effects

Two algal species have been tested with EC50 values that range from 10,500 to 509,000 µg/l (Table 8). These species are much more resistant to tetrachloroethylene than is the mysid shrimp.

Miscellaneous

As stated earlier, the 96-hour LC50 for the sheepshead minnow is between 29,400 and 52,200 µg/l (Table 9). No 96-hour LC50 could be calculated using the statistical procedures employed (U.S. EPA, 1978) since no data for partial mortality were available.

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = not available

Final Invertebrate Acute Value = 180 µg/l

Final Acute Value = 180 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = 88 µg/l

Final Plant Value = 11,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 88 µg/l

0.44 x Final Acute Value = 79 µg/l

The maximum concentration is the Final Acute Value of 180 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For tetrachloroethylene the criterion to protect saltwater aquatic life as derived using the Guidelines is 79 µg/l as a 24-hour average and the concentration should never exceed 180 µg/l at any time.

Table 6. Marine invertebrate acute values for tetrachloroethylene (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Mysid shrimp, *Mysidopsis bahia*	S	U	96	10,200	8,639

* S = static

** U = unmeasured

Geometric mean of adjusted values = 8,639 ug/l $\frac{8,639}{49}$ = 180 ug/l

Table 7. Marine invertebrate chronic values for tetrachloroethylene (U.S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Mysid shrimp, *Mysidopsis bahia*	LC	300 - 670	448

* LC = life cycle or partial life cycle

Geometric mean of chronic values = 448 ug/l $\quad \frac{448}{5.1} = 88$ ug/l

Lowest chronic value = 448 ug/l

Table 8. Marine plant effects for tetrachloroethylene

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Phaeodectylum tricornutum*	EC50	10,500	Pearson & McConnell, 1975
Alga, *Skeletonema costatum*	96-hr EC50 chlorophyll *a*	509,000	U.S. EPA, 1978
Alga, *Skeletonema costatum*	96-hr EC50 cell number	504,000	U.S. EPA, 1978

Lowest plant value = 10,500 ug/l

Table 9. Other marine data for tetrachloroethylene (U.S. EPA, 1978)

Organism	Test Duration	Effect	Result (ug/l)
Sheepshead minnow, *Cyprinodon variegatus*	96 hr	LC50	>29,400 <52,200

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion

Water. The National Organics Monitoring Survey (U.S. EPA, 1978) detected tetrachloroethylene (perchloroethylene, PCE) in 9 of 105 drinking waters sampled between November 1976 and January 1977 (range, <0.2 to 3.1 µg/l; median < 0.2 µg/l). The mean concentration of the nine positive samples was 0.81 µg/l. In Switzerland, PCE concentrations have been found in contaminated ground water as high as 954 µg/l (Giger and Molner-Kubiea, 1977). PCE was one of two halogenated compounds identified both in the drinking water and in the plasma of individuals living in New Orleans (Dowty et al. 1975). In the British Isles, municipal waters have been found to contain up to 0.38 µg PCE/l (Pearson and McConnell, 1975).

Food. PCE concentrations in seafood collected from the Liverpool Bay (England) area ranged from 0.5 to 30 µg/Kg (Pearson and McConnell, 1975; Dickson and Riley, 1976). Corresponding concentrations in the seawater were, mean 0.12 µg/l., maximum 2.6 µg/l (Pearson and McConnell, 1975). PCE concentrations in foods ranged from non-detectable amounts (<0.01 µg/kg) in orange juice to 13 µg/kg in English butter (McConnell, et al. 1975). These

data, however, apply to the British Isles. No such data appear to exist for the United States.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 49 was obtained for tetrachloroethylene using bluegills containing about 1 percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for tetrachloroethylene and the edible portion of all aquatic organisms consumed by Americans is calculated to be 49 x 2.3 = 110.

Inhalation. General environmental PCE concentrations tend to be low. Pearson and McConnell (1975) observed concentrations in city atmospheres in Great Britain to range from less than 0.68 to 68 $\mu g/m^3$. In a suburb of Munich, Loechner (1976) found concentrations of 4 µg PCE/m^3 whereas air in the center of Munich contained 6 $\mu g/m^3$. Surveys at 8 locations in the U.S. indicated concentrations up to 6.7 $\mu g/m^3$ were observed in urban areas and less than 0.013 $\mu g/m^3$ in rural areas (Lillian,et al. 1975). As with a number of related, low molecular weight, chlorinated hydrocarbon solvents by far the most significant exposure to PCE is in industrial environments (Fishbein, 1976). The major uses of PCE are in textile and dry cleaning industries (69 percent), metal cleaning (16 percent), and as a chemical intermediate (12 percent).

Dermal. As with inhalation exposures, dermal exposures of significance would be primarily confined to occupational exposure.

PHARMACOKINETICS

Absorption. Using inhalation exposure, Stewart, et al. (1961) found that PCE reached near steady-state levels in blood of human volunteers with 2 hours of continuous exposure. Such results suggest a rapid attainment of steady-state levels of PCE within the body. This may be deceptive, however, since the biological half-life of PCE metabolites (as measured as total

trichloro compounds) is 144 hours (Ikeda and Imamura, 1973). The relative stability of PCE concentrations in blood beyond 2 hours probably represents a redistribution phenomenon common to a number of volatile anesthetics (Goodman and Gilman, 1966). Later studies (Stewart, et al. 1970) have shown that PCE concentrations in expired air immediately follow exposure increase with repeated exposures over a five day period. These data confirm that steady-state implied by the leveling off of blood PCE concentrations has not been reached with short-term exposures. Retention of inhaled PCE has been estimated to approximate 57 percent of the administered dose (Ogata, et al. 1971).

Stewart and Dodd (1964) demonstrated absorption of PCE through the skin by immersion of thumbs of volunteers in PCE for 40 minutes and measurement of PCE in the exhaled air. High concentrations of PCE in exhaled breath (160 to 260 $\mu g/m^3$) were measurable 5 hours after exposure.

Distribution. Once in the body, PCE tends to distribute to body fat. Although the human data available are quite limited, in those individuals which have significant body burdens (subjects E and F in Table I.) ratios of fat to liver concentrations are greater than 6.

A more marked distribution of PCE to fat is observed using controlled exposures to rats. The data in Table 2 below (Savolainen, et al. 1977) were obtained from animals who had been exposed to 1,340 mg PCE/m^3 for 6 hours/day on 4 prior days. The zero time values represent the residual PCE from these previous exposures on the 5th day. Each succeeding time interval indicates

the kinetics of PCE buildup in each organ with the identical exposure conditions on the 5th day. As can be seen in the table, a substantial residual concentration of PCE is found in fat from the previous exposures. PCE levels rise more or less continuously with duration of exposure in brain, lungs, and fat, but tend to level out in blood and liver after a 3-hour exposure. It is notable that brain concentrations of PCE exceed blood levels by about fourfold independent of duration of the exposure. On the other hand, the ratio of concentration in fat relative to blood decreases from near 150:1 to 50:1 over the course of the exposure. These data suggest that turnover of PCE in fat is slower than that observed in other tissues.

Table 1. - Distribution of tetrachloroethylene in human tissue at autopsy (McConnell, et al. 1975)

Concentrations in ug/kg (wet tissue)

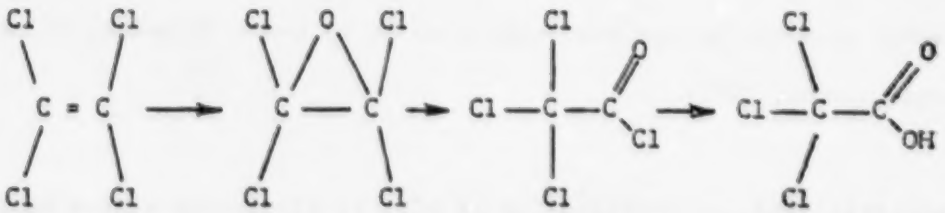
Subject	Age	Sex	Tissue	Tetrachloroethylene
A	76	F	Body fat	6
			Kidney	<0.5
			Liver	<0.5
			Brain	<0.5
B	76	F	Body fat	1
			Kidney	6
			Liver	2
			Brain	<5
C	82	F	Body fat	0.4
			Liver	1.2
D	48	M	Body fat	0.8
			Liver	0.7
E	65	M	Body fat	21
			Liver	3.4
F	75	M	Body fat	29.2
			Liver	4.3
G	66	M	Body fat	0.5
H	74	F	Body fat	4

Table 2. - Changes in the organ content of PCE with duration of exposure in rats having prior history of PCE exposure (Savolainen, et al. 1977)

Duration of Exposure (h)	Concentration*					
	Cerebrum	Cerebellum	Lungs	Liver	Perirenal Fat	Blood
0	3.1 ± 0.6	2.2 ± 0.7	1.6 ± 0.3	5.8 ± 1.5	103 ± 3	0.7 ± 0.2
2	14.9 ± 2.8	10.3 ± 1.2	7.6 ± 1.7	17.8 ± 4.5	162 ± 29	3.5 ± 0.7
3	18.0 ± 0.8	12.0 ± 0.7	8.7 ± 1.6	22.4 ± 0.2	134 ± 6	4.2 ± 0.2
4	16.8 ± 2.9	11.3 ± 0.9	9.9 ± 2.2	22.2 ± 0.1	183 ± 32	4.1 ± 0.6
6	23.7 ± 1.2	15.3 ± 0.2	12.2 ± 0.6	26.7 ± 4.0	286 ± 70	5.0 ± 1.1

* µg/g wet weight of tissue or µg/ml blood ± range of two animals.

Metabolism. Metabolism of PCE has been studied extensively in humans and experimental animals. In a qualitative sense metabolic products appear to be similar in humans (Ikeda, et al. 1972; Ikeda, 1977) and experimental animals (Yllner, 1961; Daniel, 1963; Ikeda and Ohtsuji, 1972). The metabolic pathway is summarized:



Tetrachloroethylene — Tetrachloroethylene oxide — Trichloroacetyl chloride — Trichloroacetic acid

A similar reaction has been observed when PCE is exposed to oxygen, excess chlorine, and sunlight at 36 to 40°C (Frankel, et al. 1957). It has been

postulated that the symmetrical epoxide formed from tetra-chloroethylene is not mutagenic (in E. coli K_{12}) because it is more stable and less reactive towards cellular nucleophiles than the unsymmetrical epoxides formed from vinyl chloride, 1,1-dichloroethylene and trichloroethylene, (Henschler, et al. 1976; Henschler, 1977).

Ogata, et al. (1971) report that 1.8 percent of PCE retained by humans was converted to trichloroacetic acid and 1.0 percent to an unknown metabolite in 67 hours. Metabolism of PCE is apparently saturable, in that exposures exceeding 70 mg/m^3 do not increase excretion of trichloroacetic acid in the urine (Ikeda, 1977). However, metabolism of PCE is inducible by phenobarbital (Ikeda and Imamura, 1973) and Aroclor 1254* (Moslen, et al. 1977), suggesting that a higher percentage of metabolic conversion is possible under certain conditions.

Excretion. PCE itself is primarily eliminated from the body via the lungs (Stewart, et al. 1961, 1970; Ikeda and Imamura, 1973). The respiratory half-time for PCE elimination has been estimated at 65 hours (Stewart, et al. 1970; Ikeda and Imamura, 1973).

Trichloroacetic acid, as a metabolite of PCE, is eliminated with a half-time of 144 hours via the urine (Ikeda and Imamura, 1973). Since the half-time for elimination of trichloroacetic acid as a metabolite of trichloroethylene is only 36 to 58 hours in normal humans (Ikeda and Imamura, 1973),

*Registered Trademark for a mixture of polychlorinated biphenyls

this rate is more a reflection of delayed respiratory turnover of the parent compound than for trichloroacetic acid itself. In all likelihood this is a result of the greater lipophilicity of PCE relative to trichloroethylene.

TOXIC EFFECTS

Acute, Subacute and Chronic Toxicity. As with all other members of the chloroethylene family, acute effects of PCE are very much dominated by central nervous system depression. Because of its widespread use in industry the acute central nervous system effects of PCE have been studied under controlled conditions using human volunteers. The first of these studies, by Carpenter (1937), exposed individuals to concentrations of PCE averaging 3,183 and 6258 mg/m^3 for 95 and 130 minutes, respectively. At the low concentration sensory changes and a slight feeling of elation were observed. However, at the higher concentration more definite signs of central nervous system depression were observed, i.e., lassitude, mental fogginess and exhilaration. When this concentration was raised to 10,000 mg/m^3 signs of inebriation were observed and at 13,400 mg/m^3 all were forced to leave the chamber within 7.5 minutes. Rowe, et al. (1952) reported the exposure of humans to vapor concentrations of PCE averaging 710 mg/m^3 failed to produce significant central nervous system effects whereas minimal effects could be observed at 1,340 mg/m^3.

Stewart, et al. (1961) noted impaired ability to perform a Romberg test, a measure of reflex coordination, in volunteers subjected to 1,300 mg/m^3 for

more than 30 minutes. In a later paper this same group (Stewart, et al. 1970), found that three of their subjects were not capable of performing a normal Romberg, a measure of reflex coordination, after 3 hours of exposure to 670 mg/m^3 PCE. In addition, 25 percent of the individuals reported subjective complaints ranging from mild irritation, lightheadness and mild frontal headache, to feeling slightly sleepy and experiencing some difficulty in speaking.

More recently, Stewart, et al. (1977) examined a group of 12 volunteers exposed to 168 and 670 mg PCE/m^3 for 5 1/2 hours a day repeated up to 53 days. In this study they were unable to document any consistent neurological changes due to PCE exposure, although they did observe a statistically significant decrement in the performance of a Flanagan coordination test (which the authors stated as being non-consistent). In a group of workers occupationally exposed to concentrations of approximately 400 mg/m^3 (one for 15 years) subjective complaints, such as headache, fatigue, somnolence, dizziness, and a sensation of intoxication were noted (Medek and Kovarik, 1973). In confirmation of shorter-term volunteer studies no objective neurological effects could be associated with PCE exposure.

Rowe, et al. (1952) indicated that rats, guinea pigs, rabbits and monkeys exposed repeatedly for 7 hours per day displayed no changes in behavior at vapor concentrations of PCE up to 2,720 mg/m^3. At 10,900 mg/m^3, rats were drowsy during the first week of exposure. However, in the second week marked salivation, restlessness, irritability, loss of equilibrium and

coordination were observed. Rowe, et al. (1952) suggested that this resulted from an hypercholinergic state since the excited state could be prevented by atropine.

Goldberg et. al. (1964) reported that PCE caused an 80 percent loss of both avoidance and escape responses in rats after a single 4-hour exposure to 15,400 mg/m^3. These effects were primarily attributable to an overt ataxia. In contrast, Savolainen, et al. (1977) observed increased ambulation in the open field by rats exposed to 1,340 mg/m^3 for 5 days, 6 hours daily. These changes were paralleled by a small but significant decrease in brain RNA content and an increase in non-specific cholinesterase activity. The only indications of long-term effects on the central nervous system are findings of changed EEG patterns associated with increased electrical impedence of the cerebral cortex at exposures as low as 100 mg PCE/m^3, 4 hours/day for 15 to 30 days (Dmitrieva, 1966; Dmitrieva and Kuleshov, 1971). These effects were reported to be associated with sporadic swollen and vacuolized protoplasm in some cells (Dmitrieva and Kuleshov, 1971). Although information available from experimental animals is limited, it generally supports findings of acute central nervous system depression. As in the case of human clinical studies essentially no information is available concerning long term effects (i.e., greater than one week exposures) of PCE on the central nervous system. As suggested by Stewart, et al. (1970), the current threshold limit value (ACGIH, 1977) for PCE has a negligible factor of safety even for short-term exposures. That more serious central nervous system problems may be associated with chronic PCE exposure is suggested by a few sporadic case reports

(Gold, 1969; McMullen, 1976) and small scale epidemiological and clinical studies (Coler and Rossmiller, 1953). However, the latter studies have often been complicated by exposures to other solvents (Tuttle, et al. 1977).

Short-term PCE exposures at higher concentrations, and longer exposures at lower concentrations, can produce damage to kidney and liver (Klaasen and Plaa, 1967). Increased weight and mild to marked central fatty degeneration of the liver were observed with up to 158 repeated 7-hour exposures of guinea pigs to 670 to 16,750 mg PCE/m^3 (Rowe, et al. 1952). Lower concentrations appeared to be less effective. Rabbits, rats and monkeys appeared less sensitive in that no significant effects were observed following repeated 7-hour exposures at concentrations up to 2,680 mg/m^3. Rowe, et al. (1952) indicated that at 2,680 mg PCE/m^3 increased kidney weights were also observed in guinea pigs but not in other species. However, the prior work of Carpenter (1937) had shown congestion and granular swelling in the kidney of rats exposed for 8 hours, 5 days per week over a period of 7 months to 1,540 mg/m^3. More recently, the National Cancer Institute (NCI) carcinogenesis bioassay of PCE revealed a high incidence of toxic nephropathy in both male and female B6C3-F1 mice exposed orally to 536 and 386 mg PCE/kg, respectively, for 5 days a week for 78 weeks (NCI, 1977). Similar results were obtained in both male and female Osborne-Mendel rats exposed to 471 and 474 mg PCE/kg, respectively, over the same treatment course.

Kylin, et al. (1963) noted moderate fatty degeneration of the liver with a single 240 minute exposure to 1,340 mg PCE/m^3. Exposure to this same

concentration 4 hours daily, 6 days a week for up to 8 weeks was found to increase the severity of the lesions caused by PCE (Kylin, et al. 1965).

Fujii (1975) dosed male rabbits once orally with 2,158 mg PCE/kg and observed increases in serum lipoprotein concentrations which were still evident 2 weeks after treatment. Changes in serum enzyme activities (i.e. alkaline phosphatase, glutamate-oxalacetate transaminase, glutamate-pyruvate transaminase), indicative of liver damage, were mild and transient. Single injected doses of PCE, however, will increase serum glutamate oxalacetate transaminase activity (0.3 to 2.0 ml/kg, i.p., Cornish, et al. 1973).

The data of Coler and Rossmiller (1953) involving a group of men occupationally exposed to concentrations of 1,890 to 2,600 mg PCE/m^3 supports animal data indicating that liver injury may result from PCE. Three of seven men had evidence of impaired liver function. An individual accidentally acutely exposed to an anesthetic dose of PCE exhibited a transient increase in serum glutamate-oxalacetate transaminase activity and a delayed elevation of urinary urobilinogen, both indicative of hepatic injury (Stewart, 1969).

The possible cardiovascular effects of PCE have not been systematically investigated. Unlike its analog, trichloroethylene, PCE does not appear to sensitize the myocardium to epinephrine (Reinhardt, et al. 1973). However, in controlled human studies involving exposure to PCE at 1140 mg/m^3 for 3 hours Ogata, et al. (1971) indicated an increase of diastolic blood pressure averaging 15 mm Hg compared to a decrease of 5 mm Hg in a non-exposed group

over the same time interval. Systolic blood pressure changed only slightly in both groups (+2 mm Hg with PCE and -4 mm Hg in controls). Although not specifically addressed in the discussion of the results, a group of six volunteers exposed to 1,300 mg PCE/m^3 for 187 minutes uniformly showed an increase in systolic blood pressure which averaged 15 mm Hg (Stewart, et al. 1961). Other groups exposed to the same concentration for only 83 minutes or to a lower concentration of PCE (670 mg/m^3), showed no consistent change in blood pressure.

PCE, as with a number of other low molecular weight chlorinated compounds, greatly increases bile duct-pancreatic fluid flow in rats (Hamada and Peterson, 1977). The resulting fluid has a markedly depressed protein content and a significantly altered ionic composition. The physiological significance of these observations has not yet been determined.

Occasional reports have associated PCE with the symptomatology of more serious chronic diseases such as Raynaud's disease (Lob, 1957; Sparrow, 1977). Sparrow (1977) has reported a case which involved depressed immune function, mildly depressed liver function, polymyopathy and severe acrocyanosis. Such isolated reports are difficult to evaluate, but deserve mention here because of a similar disease which has been observed in vinyl chloride workers. Vinyl chloride, or monochloroethylene, is closely related to PCE.

Synergism or Antagonism. As PCE is metabolized by mixed function oxidases, compounds which alter the functional activity of this system might

be expected to affect its toxicity. Cornish, et al. (1973a, 1977), however, were unable to demonstrate that phenobarbital pretreatment was capable of modifying the hepatotoxicity of PCE. Moslen et al. (1977) and Reynolds and Moslen (1977) report that PCE produces vacuolization of rough endoplasmic reticulum and increases in serum glutamate oxalacetate transaminase activity following Aroclor 1254* induction of mixed function oxidases. It must be kept in mind that only a small percent of retained PCE is metabolized when compared to other members of the chloroethylene series (Ogata, et al. 1971). Consequently, both the experiments conducted by Cornish, et al. (1973, 1977) and Reynolds and Moslen (1977) were of too short duration to fully assess the influence of metabolism on the long-term toxicity of PCE.

Intolerance of alcohol has been reported with PCE exposure (Gold, 1969). As both compounds are central nervous system depressants such effects are to be expected. There do not appear to be any documented metabolic interactions of PCE with alcohol as there are with trichloroethylene (Cornish and Adefuin, 1966; Gessner, 1973). Stewart, et al. (1977) were unable to document any significant interactions between alcohol or diazepam with PCE exposures up to 670 mg/m^3. However, the question of synergism between ethanol and PCE has not been addressed experimentally over a sufficiently large dose range to rule out such an interaction.

*Registered Trademark for a mixture of polychlorinated biphenyls

PCE interactions with benzene and toluene have been studied systematically with lethality as an endpoint (Withey and Hall, 1975). Intubation of rats with mixtures of benzene and PCE yielded a combined toxicity which was only slightly less than additive. Mixtures of toluene and PCE resulted in LD_{50} values of less than that predicted for simple additivity, indicating synergistic effects.

Since PCE is metabolized to trichloroacetic acid there may be a possibility of its synergizing with compounds, such as warfarin, that bind significantly with serum albumin (Wardell, 1974). Although this has been suggested for trichloroethylene (Ertle, et al. 1972), this question has not been systematically investigated with PCE.

Mutagenicity. Henschler (1977a, b) and coworkers have postulated that the mutagenicity and carcinogenicity of chloroethylenes are dependent upon the reactivity of their metabolically formed epoxide intermediates. Unsymmetrically substituted chlorines result in unbalanced electron withdrawal by chlorine atoms and a more reactive epoxide intermediate. Support for this hypothesis is gained from the demonstration of an increased rate of spontaneous mutation in E. coli K_{12} in the presence of liver microsomes when treated with chloroethylene (vinyl chloride), 1,1-dichloroethylene, and trichloroethylene and an absence of increased rate of mutation with the symmetrically substituted 1,2-dichloroethylenes and tetrachloroethylene (Greim, et al. 1975). Comparison of the compounds using Salmonella typhimurium was said not to be

possible because of a high primary toxicity of some of the compounds (Henschler, 1977a, b). Nevertheless, Cerna and Kypenova (1977) indicate finding elevated mutagenic activity in Salmonella strains sensitive to both base substitution and frameshift mutation treated with PCE and cis-1,2-DCE, both symmetrically substituted compounds.

Bonse,et. al. (1975) has shown that tetrachloroethylene oxide was reasonably stable but that the trichloroacetyl chloride formed from the epoxide was highly reactive. The acyl halide was found to covalently bind with cellular constituents. This may account for the discrepancy of the prediction of Henschler (1977) regarding the carcinogenicity of PCE (NCI, 1977).

Teratogenicity. Only one report has appeared concerning the possibility of PCE-induced teratogenesis (Schwetz, et al. 1975). Female rats and mice were exposed to 2000 mg PCE/m^3 7 hours daily on days 6 to 15 of gestation. Primary effects of PCE included a decrease in fetal body weight of mice, a small but significant increase in fetal resorptions in the rat, subcutaneous edema in mice pups, and delayed ossification of skull bones and sternabrae in the mice. These effects were mild, leading the authors to conclude that PCE was not teratogenic. However, it must be pointed out that these experiments were conducted with only one dose, which was only three times greater than the current TLV and involved intermittent (i.e., 7 hr/day) exposure to the chemical during a limited segment (10 days) of a short gestational period (21 days). If PCE behaves in mice as it does in humans, at least 5 days exposure

would be necessary to achieve steady-state concentrations in the animal. Although the effects were minor, they were statistically significant. Additional work is necessary to clarify whether PCE possesses teratogenic activity.

Carcinogenicity. PCE has been demonstrated to be a liver carcinogen in B6C3-F1 mice (NCI, 1977). Results in Osborne-Mendel rats were negative, but a high rate of early mortality precluded use of rat data in evaluating the carcinogenicity of PCE. Furthermore, recent data in which carbon tetrachloride was used as a positive control revealed that Osborne-Mendel rats have a low sensitivity to induction of hepatocellular carcinoma by chlorinated organic compounds in general (NCI, 1976).

The only tumor which occurred in either male or female B6C3-F1 mice that could be related to PCE administration was hepatocellular carcinoma. These data are depicted below.

Table 3. - Incidence of hepatocellular carcinoma in PCE-treated B6C3F-1 mice (NCI, 1977)

	Males	Females
Control	2/17	2/20
Vehicle Control	2/20	0/20
Low dose	32/49 (536 mg/kg)	19/48 (386 mg/kg)
High dose	27/48 (1072 mg/kg)	19/49 (772 mg/kg)

Low dose males received a time weighted average dose of 536 mg/kg, 5 days/ week for 78 weeks. High dose males received 1072 mg/Kg on the same schedule. Low dose and high dose female groups received 386 and 772 mg/kg, also on the same schedule.

No systematic studies of PCE exposure and the incidence of human cancer seem to be available.

CRITERION FORMULATION

Existing Guidelines and Standards

Existing tetrachloroethylene (PCE) standards are primarily applicable to occupational exposures. The present American Governmental Conference on Industrial Hygiene threshold limit value (TLV) listed in Table 4, has been established primarily on the basis of measurable deficits in central nervous system function resulting from short-term exposures of healthy male volunteers. As Stewart, et al. (1970) point out this figure incorporates a negligible factor of safety even for this group. Thus, sensitive populations or the possibility of other environmental conditions which might synergize with PCE toxicity have not been considered (AGCIH, 1977). Additionally, it does not yet incorporate consideration of PCE carcinogenicity (NCI, 1977).

TABLE 4
Industrial hygiene standards for tetrachloroethylene in various countries (Fishbein, 1976)

	mg/m^3	Calculated Allowable Daily Exposure mg/day
USA	670	4793
German Democratic Republic	250	1786
USSR	1	7

Current Levels of Exposure

The National Organics Monitoring Survey (U.S. EPA, 1978) detected tetrachloroethylene (perchloroethylene, PCE) in 9 of 105 drinking waters sampled between November 1976 and January 1977 (range, $<$ 0.2 to 3.1 µg/l; median $<$ 0.2 µg/l). The mean concentration of the nine positive samples was 0.81 µg/l. PCE was one of two halogenated compounds indentified both in the drinking water and in the plasma of individuals living in New Orleans (Dowty, et al. 1975).

No data were found on levels of PCE in United States food. In England, PCE concentrations in foods ranged from non-detectable amounts ($<$0.01 µg/kg) in orange juice to 13 µg/kg in English butter (McConnell, et al. 1975).

General environmental PCE concentrations tend to be low. Surveys at eight locations in the U.S. found concentrations of up to 6.7 $\mu g/m^3$ in urban areas and less than 0.013 $\mu g/m^3$ in rural areas (Lillian, et al. 1975). By far the most significant exposure to PCE occurs in industrial environments (Fishbein, 1976). The major uses of PCE are in textile and dry cleaning industries (69 percent), metal cleaning (16 percent), and as a chemical intermediate (12 percent). As with inhalation exposures, dermal exposures of significance would be primarily confined to occupational exposure.

Basis and Derivation of Criterion

No additional human or animal data exist that may be used to refine the AGCIH estimate of non-carcinogenic risks from exposure to PCE, with the exception of the data of Dmitrieva (1966) and Dmitrieva and Kuleshov (1971). These Russian papers suggest that central nervous system effects

can be observed in rats at exposures to PCE as low as 100 mg/m^3 in an experiment lasting 5 months. Using these authors' data, the following acceptable daily intake for non-carcinogenic risk may be calculated for PCE according to the method of Stokinger and Woodward (1958):

$$\frac{0.000073\ m^3/min \times 60\ min \times 5\ hr \times 10\ mg/m^3 \times 0.57 \times 70\ kg}{0.4\ kg \times 100} = 0.218\ mg/day$$

Where:

0.000073 m^3/min = Minute volume of the rat (Altman and Dittmer, 1974).

60 x 5 hr = Duration of daily exposure (Dmitrieva,1966).

10 mg/m^3 = Air concentration of PCE at which there was no observable effect (Dmitrieva, 1966).

0.57 = Coefficient of absorption by the inhalation vs. ingestion route (Ogata, et al. 1971).

70 kg = Average body weight for an adult male.

0.4 kg = Estimated body weight for adult rat.

100 = Safety factor.

The safety factor of 100 was based on the rationale developed in the National Academy of Science Report on Drinking Water and Health (NAS, 1977). The general guideline applied to compounds with limited human studies and valid animal studies was adopted. Based on the above calculation and assuming a 2 liter daily consumption of drinking water, concentrations of PCE in drinking water should be limited to 110 µg/l.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Tetrachloroethylene is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of tetrachloroethylene in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of tetrachloroethylene corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.020 µg/l	0.20 µg/l	2.0 µg/l
Consumption of fish and shellfish only.	0	0.040 µg/l	0.40 µg/l	4.0 µg/l

(1) Calculations by applying a modified "one-hit" extrapolation model decribed in the Methodology Document to the animal bioassay data presented in Appendix I and in Table 3. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 51 percent of the tetrachloroethylene exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 110-fold. The remaining 49 percent of tetrachloroethylene exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of tetrachloroethylene, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding tetrachloroethylene concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding tetrachloroethylene concentrations. Because data indicating other sources of tetrachloroethylene exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

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Appendix I

Derivation of Criteria for Tetrachloroethylene

Tetrachloroethylene administered by gavage to mice caused hepatocellular carcinomas in both males and females in the NCI bioassay at both the high and low dose levels. The females were treated at 772 and 386 mg/kg five times per week for 78 weeks and held until 90 weeks for observation. In females of the high dose group the lifetime probability of dying of hepatocellular carcinoma was 0.938, whereas the matched vehicle and matched untreated controls had an incidence of hepatocellular carcinoma indistinguishable from that of pooled controls, which was 6/196. The lifetime probability given in the NCI report is used for the water criteria documents rather than the actual incidence because a correction is needed for the excess early deaths in the treated groups due to kidney toxicity. With a fish bioaccumulation factor of 110, the parameters of the extrapolation model are:

$n_t/N_t = 0.938$	le = 78 weeks
$n_c = 6$	d = 772 x 5/7 = 551 mg/kg/day
$N_c = 196$	w = .026 kg
Le = 90 weeks	L = 90 weeks
	R = 110

The result is that the water concentration should be less than 2.2 micrograms per liter (2.16 µg/l) in order to keep the individual lifetime risk below 10^{-5}.